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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/828,986	04/20/2004	Michael T. Barrett	10031482-1	7617

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EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/828,986	BARRETT ET AL.	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31 and 34* is/are pending in the application.

4a) Of the above claim(s) *7-24,30 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 25-29 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/8/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed September 8, 2006. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Claims 1-31 and 34 are currently pending. Claims 7-24 and 30-31 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim.

Claims 1 and 28 have been amended. Claim 34 is newly presented. Therefore Claims 1-6, 25-29, and 34 will be addressed herein.

Information Disclosure Statement

2. The information disclosure statements (IDS) submitted on September 8, 2006 has been considered. The Huang et al reference which has a line drawn though it has been considered but has a line drawn through it because it also appeared on the IDS form submitted on April 20, 2004.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

THE FOLLOWING IS A NEW GROUND OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

In the instant case the specification does not appear to provide support for the amendment made to claim 1 which recites "and which hybridizes under stringent hybridization conditions". It is noted that the applicant points to the specification at pages 13, lines 4-8; page 14, lines 19-21; and page 8 lines 28 to page 9 line 7 for support. The specification teaches on page 13 that a CpG UNA is an oligonucleotide that a) contains at least one UNA nucleotide and therefore has reduced secondary structure and b) corresponds to i.e. has a sequences that is at least partially complementary to or the same as and will base pair with a CpG island. This definition does not require that the CpG UNA hybridize under stringent conditions with a CpG island. The teachings on page 14 of the specification further define the term "CpG island", however once again there is no mention of hybridization under stringent conditions. The teachings on page 8 define the term "stringent hybridization" but do not suggest that a CpG UNA will only hybridize under stringent conditions with a CpG island. Thus while the specification provides support for a CpG UNA which has a

sequence which is at least partially complementary to or the same as a CpG island, the specification does not provide specific support for a CpG UNA which hybridizes under stringent conditions with a CpG island.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

THE FOLLOWING IS A NEW GROUND OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6 are indefinite over the recitation of the phrase "A CpG unstructured nucleic acid oligonucleotide containing at least one UNA nucleotide which hybridizes...". This phrase in considered indefinite because it is unclear if any part of the CpG UNA can hybridize to the CpG site or if the actual UNA nucleotide has to hybridize to the CpG site.

Claims 1-6 are indefinite over the recitation of the phrase "stringent hybridization". This phrase in considered unclear because "stringent hybridization" is not defined by the claim or the specification, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. While pages 8 and 9 of the specification provide several examples of stringent hybridization conditions a complete

definition for this term is not provided. Therefore it is unclear if the claims which recite "stringent conditions" are limited only to the conditions listed in the examples and if so which example or if additional hybridization conditions meet this limitation. Since the specification only provides examples of what could be included by this phrase, these teachings are not considered to be sufficient to provide a complete and fixed definition for the phrase "stringent hybridization".

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

THE FOLLOWING IS A NEW GROUND OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang (US Patent 6605432 Filed 2000) in view of Kutyavin et al (US Patent 5912340 Issued 1999).

Regarding Claim 1 Huang teaches an array comprising CpG dinucleotide rich probes. These CpG dinucleotide rich probes affixed to the solid support of the screening array are employed to identify the presence or absence of methylated sites (Column 7). Huang further teaches a method comprising: subjecting a nucleic acid

sample to a methylation sensitive restriction enzyme which digests unmethylated CpG sites leaving methylated CpG sites in tact, amplifying the methylated CpG fragments, and hybridizing the amplicons to the CpG probe array. Amplicons which are complementary to the probe sequences on the CpG array will produce a positive hybridization signal (column 14). Further Haung teaches that array contains at least 1000 CpG probes (Column 9). Thus Huang teaches an array of probes which hybridize to CpG sites.

Huang does not teach that the CpG probes contain at least one unstructured nucleic acid.

However Kutyavin et al teach probes which contain unstructured nucleic acids (Abstract and Table 2). Specifically Kutyavin et al teach probes which comprise nucleotides G' (6-oxo-purine (hypoxanthine)), C' (pyrrolo-[2,3-d]pyrimidine-2(3H), A' (2-aminoadenine) and T' (2-thiothymine). The modified bases are capable of forming a stable base pair with their natural base partner, but are unable to form a stable base pair with their modified base partner (Abstract, Columns 6-8). Thus Kutyavin et al teach that G' and C' and A' and T' base pair with each other at a stability that is lower than that of G and C and A and T. Additionally it is noted that it is an inherent property that nucleic acids which contain unstructured nucleic acids have reduced secondary structure.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the array of probes taught by Huang by changing the probes of Huang so that the modified probes contain at least one

unstructured nucleic acid as suggested by Kutyavin et al. The probes of Kutyavin allow for the reduction of the formation of secondary structures between adjacent probes which can interfere with the hybridization between the probe and the target. Thereby modifying the probes of Huang would have allowed for a more effective means for detecting CpG sites.

6. THE FOLLOWING IS A NEW GROUND OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

Claims 25-29 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang (US Patent 6605432 Filed 2000) in view of Kutyavin et al (US Patent 5912340 Issued 1999) and in further view of Ahern (The Scientist 1995).

The teachings of Huang and Kutyavin et al are presented above in paragraph 5.

Regarding Claims 25-29 and 34 the combined references teach an array comprising CpG UNA probes. Further Huang teaches a method comprising contacting sample nucleic acid with a methylation sensitive restriction enzyme to produce a target composition and assessing the binding of said target to the probe array (Column 14). Additionally Haung further teaches a method comprising contacting a control nucleic acid (derived from a non cancer cell) and a test nucleic acid (derived from a cancer cell) with a methylation sensitive restriction enzyme to produce a first and second set of target compositions, contacting the first set of target compositions to a first array, contacting the second set of target compositions to a second array, and comparing the binding between both sets (column 16).

However the combined references do not teach packaging the CpG UNA array and instructions for its use into a kit. However, reagent kits for performing hybridization assays were conventional in the field of molecular biology at the time the invention was made. In particular, Ahern discloses the general concept of kits for performing detection methods and teaches that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Ahern (page 22) also teaches that kits provide the benefits of cost-effectiveness and time efficiency. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the CpG UNA array and instructions for its use into a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect CpG methylation.

Additionallly it is noted that claims 28 and 34 have been amended to recite partiuclar instructions to include in the kits. Printed matter in kits such as instructions are not given any patentable weight. Please refer to MPEP 2112.02 III.

7. THE FOLLOWING IS A NEW GROUND OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang (US Patent 6605432 Filed 2000) in view of Sampson (US 2005/0032055 Filed 4/2003).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Regarding Claim 1 Huang teaches an array comprising CpG dinucleotide rich probes. These CpG dinucleotide rich probes affixed to the solid support of the screening array are employed to identify the presence or absence of methylated sites (Column 7). Huang further teaches a method comprising: subjecting a nucleic acid sample to a methylation sensitive restriction enzyme which digests unmethylated CpG sites leaving methylated CpG sites in tact, amplifying the methylated CpG fragments, and hybridizing the amplicons to the CpG probe array. Amplicons which are complementary to the probe sequences on the CpG array will produce a positive

hybridization signal (column 14). Further Haung teaches that array contains at least 1000 CpG probes (Column 9). Thus Huang teaches an array of probes which hybridize to CpG sites.

Huang does not teach that the CpG probes contain at least one unstructured nucleic acid.

However Sampson teaches probes which contain unstructured nucleic acids (Abstract). Specifically Sampson teaches probes which comprise nucleotides G', C', A' and T'. Sampson further teaches that base pair analogs (A'/T' and G'/C') are unable to form a stable base pair, however A', T', G', and C' are capable of forming stable base pairs with A, T, G, and C (Para 0062). Thus Sampson et al teach that G' and C' and A' and T' base pair with each other at a stability that is lower than that of G and C and A and T. Additionally Sampson teaches UNAs have reduce levels of secondary structure because of their reduce ability to form intramolecular hydrogen bond base pairs between regions of substantially complementary sequences (Abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the array of probes taught by Huang by changing the probes of Huang so that the modified probes contain at least one unstructured nucleic acid as suggested by Sampson et al. The probes of Sampson allow for the reduction of the formation of secondary structures between adjacent probes which can interfere with the hybridization between the probe and the target. Thereby modifying the probes of Huang would have allowed for a more effective means for detecting CpG sites.

8. THE FOLLOWING IS A NEW GROUND OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

Claims 25-29 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang (US Patent 6605432 Filed 2000) in view of Sampson (US 2005/0032055 filed 4/2003) and in further view of Ahern (The Scientist 1995).

The teachings of Huang and Sampson are presented above in paragraph 7.

Regarding Claims 25-29 and 34 the combined references teach an array comprising CpG UNA probes. Further Huang et al teach a method comprising contacting sample nucleic acid with a methylation sensitive restriction enzyme to produce a target composition and assessing the binding of said target to the probe array (Column 14). Additionally Haung further teaches a method comprising contacting a control nucleic acid (derived from a non cancer cell) and a test nucleic acid (derived from a cancer cell) with a methylation sensitive restriction enzyme to produce a first and second set of target compositions, contacting the first set of target compositions to a first array, contacting the second set of target compositions to a second array, and comparing the binding between both sets (column 16).

However the combined references do not teach packaging the CpG UNA array and instructions for its use into a kit. However, reagent kits for performing hybridization assays were conventional in the field of molecular biology at the time the invention was made. In particular, Ahern discloses the general concept of kits for performing detection methods and teaches that kits provide the advantage of pre-assembling the specific

reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Ahern (page 22) also teaches that kits provide the benefits of cost-effectiveness and time efficiency. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the CpG UNA array and instructions for its use into a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect CpG methylation.

Additionallly it is noted that claims 28 and 34 have been amended to recite partiuclar instructions to include in the kits. Printed matter in kits such as instructions are not given any patentable weight. Please refer to MPEP 2112.02 III.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

DIANA JOHANNSEN
PRIMARY EXAMINER